Up to Date and Perspectives for Hepatocellular Carcinoma's Intraoperative Ultrasound From Contrast Enhanced Intraoperative Ultrasound and Intraoperative Elastography to Ultrasound Guided Liver Resections

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Rezumat

Actualități și perspective în ecografia intraoperatorie a hepatocarcinomului: de la ecografia cu substanță de contrast și elastografie intraoperatorie la rezecțiile hepatice ghidate ecografic

Cu tot progresul tehnologic înregistrat până în prezent, hepatocarcinomul reprezintă încă o provocare diagnostică și terapeutică, managementul optim fiind asigurat doar de o atitudine personalizată, oferită de o abordare multidisciplinară. Ecografia are un rol esențial în ghidurile de conduită pentru această neoplazie, aplicarea intraoperatorie fiind obligatorie pentru creșterea supraviețuirii acestor pacienți, atunci când abordarea chirurgicală este posibilă și indicată. Lucrarea de față subliniază principalele indicații ale ecografiei intraoperatorii pentru diagnosticul și tratamentul hepatocarcinomului, împreună cu domeniile ce au potențial de dezvoltare.

Cuvinte cheie: hepatocarcinom, ecografie intraoperatorie, tehnici ablativă, rezecții hepatice ecoghidate, elastografie

Abstract

With all the technological progress registered so far, hepatocellular

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carcinoma is still a diagnostic and therapeutic challenge, the optimal management being ensured only by a personalized attitude, offered by a multidisciplinary approach. Ultrasound plays an essential role in the guidelines for this neoplasm, the intraoperative application being mandatory to increase the survival of these patients, when the surgical approach is possible and indicated. This paper highlights the main indications for intraoperative ultrasound in the diagnosis and treatment of hepatocellular carcinoma, along with areas that have developmental potential.

Key words: hepatocellular carcinoma, intraoperative ultrasound, ablative techniques, ultrasound guided resections, elastography

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death in the world, with increasing incidence. It is associated with a survival of only 10-15% at 5 years, mainly due to its diagnosis in advanced stages (1). 70-90% of HCC cases occur on a cirrhotic liver (2). The only treatment with curative intent in the case of early-stage HCC, with a survival of up to 50-70% at 5 years is the surgical treatment (liver resections, liver transplantation) and ablative techniques (3).

Current indications for liver resections are tumors developed on a non-cirrhotic liver or small size HCC, developed on a compensated cirrhotic liver (without the presence of portal hypertension). In the case of multicentric HCC, of the presence of major vascular invasion or portal hypertension, the morbidity, prognosis, and possibility of alternative therapies should be taken in account (4).

Ablative techniques, by radio frequency or microwave, are an effective treatment for tumors under 3 cm, with a very good prognosis in patients with altered liver function and/or clinical status that contraindicates surgical treatment (5). However, beyond the standard indications, survival has been improved by using these techniques even in more advanced cases, as ablation can control the progression of the disease or increase patients' eligibility for curative treatment (liver transplant) (6).

Intraoperative ultrasound (IOUS) is an essential tool in hepatobiliary oncological surgery, being a valuable and indispensable

imaging technique that offers excellent spatial and contrast resolution, with the possibility of visualizing images in real time, being useful in verifying and confirming preoperative imaging diagnosis and especially in guiding the therapeutic conduit, both in classical and laparoscopic surgery, even allowing changes in the process of therapeutic decision during surgery. Hepatic IOUS plays an essential role in the correct description of liver lesions, topography and loco-regional extension, relationships with neighboring anatomical structures and in the staging of the disease, being used in patients with HCC since early '70s (7).

In the current article we want to illustrate in a narrative way the main up-to-date applications of IOUS in the surgical treatment of HCC, together with perspective techniques in the field: minimally invasive approach, contrast enhanced intraoperative ultrasound (CE-IOUS) and elastography.

Elements of Technique and Approach Methods

Necessary equipment

Ideally, ultrasound machines used in the operating room should be compact, mobile, easy to handle and to provide high-quality images (8). Now a days there is a wide selection of accessories used in IOUS: probes of different types, with appropriate shape and with a specific purpose, depending on each case, taking in account the type and location of the lesions. Standard transducers for transabdominal ultrasound can also be used, but there are

some limitations in terms of image resolution and the large size of the transducer who does not provide optimal handling space (9). However, these conventional transducers can be used at the beginning of the liver examination, to obtain an overview of the anatomy of the organ (9,10). The transducers used in IOUS operate at a high frequency (between 7.5-10 MHz), thus allowing a very good spatial and detailed resolution (8). Transducers of different shapes are available for intraoperative use: linear T-shaped probes, interdigital probes, micro convex probes, T-shaped probes with trapezoid scanning window (11). In the case of liver surgery, the ideal transducer is a small one, which can be easily manipulated in narrow spaces (inter-hepato-phrenic space) and due to the ergonomic design, will allow the operator to have permanent contact with the liver surface, without the possibility to miss some areas (10,12) (*Fig. 1*).

IOUS can also be used in laparoscopic surgery, dedicated transducers being available for this type of approach, with a typical frequency between 5-10 MHz, linear or convex "side-wire" models, mounted at the end of a long and thin articulated arm, of whose design allows insertion and manipulation through trocars. In the best scenario, the IOUS equipment used in liver surgery should ensure the possibility of using contrast enhanced ultrasound, elastography, pulsed Doppler ultrasound and color/power Doppler.

Figure 1. Intraoperative ultrasound of the liver using a micro-convex intraoperative probe (Hitachi Aloka) (from personal files of the authors)

Examination technique / approaches

Ideally, in the operating room, the ultrasound machine should be positioned in front of the main operator, in order to simultaneously view both the ultrasound monitor and the operating field, respecting a principle of collinearity between surgeon, liver and monitor. Liver exploration should always begin with the inspection and palpation of it and of the entire peritoneal cavity, steps that should not be omitted in favor of IOUS, as they continue to play a very important role in liver cancer surgery (13). In order to have enough space to handle the transducer and to be able to scan the entire surface of the liver, it is necessary to mobilize the liver by initially cutting the round and falciform ligament and later on the triangular and coronary ligaments. By pulling the round ligament, the surface of the liver is exposed and the liver can be scanned systematically and completely by following portal pedicles and suprahepatic veins (11).

The cirrhotic liver represents a challenge when put in front of a differential diagnosis between regeneration nodules and a real neoplasm (HCC). In these situations, CE-IOUS plays an essential role by characterizing the vascular pattern of cirrhotic nodules, thus making it possible to differentiate between regenerating nodules and malignant tumors (14). Typical for HCC, CE-IOUS indicates a hyperenhancement in the arterial phase and a specific "wash out" of the contrast substance during the venous and late phase, when the tumor appears hypoechoic (15,16). Another vascular pattern corresponding to poorly differentiated HCC is characterized by a hypoechoic pattern with a basket-like peripheral arterial neovascularization (17).

Applications of IOUS in HCC surgery

Intraoperative diagnosis/staging

IOUS has a role in the detection and differential diagnosis of liver lesions (benign versus malignant), in the characterization of lesions, their topography and loco-regional extension, in establishing relationships with neighboring

anatomical structures and in staging the disease.

In addition to intraoperative confirmation of the lesion, the literature shows that IOUS reveals new lesions in 30% of patients with cirrhotic liver (18). However, most nodules detected by IOUS in cirrhotic patients are not tumoral lesions, conventional IOUS (gray scale) having a risk of overestimation in these situations. In these patients, an essential role is played by CE-IIOUS and elastography, methods that allow the characterization of lesions according to the vascular pattern and tissue elasticity (19).

The advantage brought by the option of intraoperative restaging of the lesions consists in the possibility to modify in real time the surgical therapeutic approach by performing a more extensive resection or on the contrary by taking a more conservative attitude (eg ablative techniques).

IOUS guided liver resections

During liver resection, the standard radical treatment for HCC, in addition to obtain oncological and functional optimal results, special care should be paid to liver parenchyma preservation, the liver function of cirrhotic patients being usually altered and therefore, the remaining liver volume being an important prognostic factor after resection (20–22).

In modern liver surgery, both for the treatment of HCC and for colorectal liver metastases, the use of IOUS allows the surgeon to perform the so-called "radical but conservative surgery". (23) Practically, by obtaining information about the relationships that the liver lesions have with intrahepatic bilio-vascular structures in real time (by IOUS), the surgeon can guide his resection line, respecting the Glissonian pedicles and suprahepatic veins and by that, preserving as much functional liver parenchyma as possible (10,24,25). This is not possible in classical liver surgery, when resections are based on conventional, descriptive, surface landmarks.

Another major advantage of IOUS is related to the possibility of performing anatomical resections. This principle is based on the

anatomy of the liver, in relation to the afferent and efferent vascularization, the exact segmental limits being different from individual to individual, with a contour "in geographic map shape". The benefits of an ideal, anatomical resection are translated into reduced blood loss (because the afferent pedicle is primarily intercepted), a reduced risk of necrosis on the resection parenchyma (because all tissue vascularized by that pedicle is removed) and a reduced risk of micro-satellite metastases recurrence. This technique involves compression to the segmental portal branches corresponding to the targeted area (usually between the transducer and the operator's fingers), thus resulting in a transient ischemia of the parenchyma; the limits can be marked with electrocautery and subsequently, the resection is performed along the previously marked line (24,26–29) (*Fig. 2*).

IOUS is currently considered as the standard method for guided liver resections. The introduction of CE-IIOUS brought major advantages in the evolution of liver surgery, but the technique has the disadvantage of short period of time visualization of the lesion and cannot be used as a navigation tool or to guide the liver resections, this being time consuming (30).

In this idea, the technological contribution facilitated another useful technique for the operator to guide his liver resection: indocyanine green fluorescence imaging technique (ICG-FI). Extrahepatic bile ducts, liver tumors and liver segments can be highlighted based on the fluorescence property of ICG (water-soluble molecule) and its rapid excretion by bile. In practice, ICG is administered intravenously before or during the surgery, at variable intervals, and "illuminates" the surface of the liver when it comes in contact with the infrared light source (31). One of the advantages of using ICG-FI is that it also provides accurate information in the case of liver cirrhosis, in contrast to other substances used for ultrasound guidance: portal hypertension can obstruct ultrasound-guided liver mapping (32). However, the visualization of tumors using ICG-FI is limited by the depth

Figure 2. Anatomical ultrasound guided resection of liver's segment VI (from personal files of the authors): **(A)** Ultrasound guided compression of glissonian pedicle (arrows) between transducer and surgeon's finger (star); **(B)** Ischemic delimitation of segment VI, consecutive to finger-transducer compression;

of penetration of infrared light and the thickness of liver tissue: infrared light can penetrate the tissue only up to 5-10 mm and the tumors located deep inside the parenchyma cannot be visualized (33).

Despite the potential benefits that ICG-FI can bring in hepato-biliary surgery, CE-IOUS remains the gold standard for liver mapping, and more studies are needed to assess the sensitivity and specificity of this method, currently used as a complementary technique (31).

Guiding ablative techniques

Interventional therapies are an alternative method of treatment used to control the progression of the disease or to increase patients' eligibility for curative treatment. In the last decades, technological innovations have yielded important results in prolonging survival through the use of local ablative techniques (6).

Using advanced percutaneous techniques or combining ablative techniques with other therapies (intraarterial chemotherapy) has increased the number of cases with treatable HCC, cases initially considered borderline or feasible only for palliative treatment (34).

Radiofrequency (RF) or microwave (MWA) ablations are indicated in patients who are not suitable for surgical resection due to impaired liver function, for unresectable HCC or in

patients who are on the waiting list for liver transplantation. There are several ways through which these techniques can be used: percutaneous, by laparotomy or by laparoscopy (35).

There are studies that have shown that short- and long-term outcomes in patients treated by percutaneous ablation are similar to those treated through surgery (36). It emphasizes that ablative surgical techniques are a feasible treatment alternative for tumors whose percutaneous approach is difficult or not possible (37). These ablative techniques can be combined with liver resections or can be staged performed after surgical resections, contributing to the completion of oncological requirements (38).

Laparoscopic ablation is a minimally invasive treatment alternative, indicated when percutaneous ablation is not feasible and when laparotomy is contraindicated or too invasive (39). Of course, laparoscopic surgery comes with several disadvantages related to the evaluation of the liver, the surgeon losing the ability to palpate structures and lesions. IOUS manages to compensate these disadvantages, providing highly useful intraoperative imaging and greater sensitivity in detecting liver lesions than most preoperative imaging techniques cannot see. Laparoscopic intraoperative ultrasound has a sensitivity and

Figure 3. Laparoscopic intraoperative ultrasound of a hepatocellular carcinoma of segment V. (from personal files of the authors)
(A) Intraoperative aspect, with the laparoscopic transducer (Hitachi Aloka); **(B)** Ultrasound aspect of the tumor, in contact with the gallbladder.

specificity similar to that of open surgery (40) (*Fig. 3*).

Regardless of the approach chosen for performing these ablative techniques, IOUS is used to locate the tumors, as a tool to guide the intervention, to avoid damage to vascular or biliary structures and adjacent organs, allowing the insertion of the ablation needle under direct view. Last but not least, IOUS is essential to assess the effectiveness of treatment: the area of necrosis after ablation and possible complications (41). Performed under these conditions, guided ablations with the help of IOUS are safe, well tolerated, being an effective treatment option which provides excellent local control of primary liver tumors (41). Moreover, in the case of small HCC, studies show that intraoperative RFA has a local recurrence rate equivalent to that following surgical resections (42).

Intraoperative contrast enhanced ultrasound

The possibility of performing CE-IOUS has an important role in the treatment of HCC. Currently, the contrast agents used are SonoVue (gaseous sulfur hexafluoride; Bracco, Milan Italy) and Sonazoid (gaseous perflubutane; GE Healthcare, Norway/DaiichiSankyo, Japan), both effective for characterizing liver lesions and for differentiating benign from malignant lesions (10,43,44). These intravascular contrast agents offer the possibility of continuous, real-time monitoring of intravascular uptake, which has led to their widespread use. The gas-filled microbubbles of these agents tolerate low acoustic pressures, enabling continuous observation during the arterial phase and repeated scanning during the late phase (24).

CE-IOUS is additional for surgical navigation and provides the surgeon essential information for the diagnosis and staging of the disease (45,46), being considered the most useful imaging technique in the surgical treatment of HCC (47).

The literature indicates that there are no statistically significant differences between CE-IOUS and MRI in terms of the ability to make a differential diagnosis of liver tumors (48). CE-IOUS can accurately characterize the vascular pattern of liver nodules, thus contributing to differentiate the regenerative nodule from the neoplastic ones (14) (*Fig. 4*).

The contrast agent available and used in Europe is made of sulfur hexafluoride microbubbles stabilized by a phospholipid shell (SonoVue, Bracco Imaging, Milan, Italy). As a method of examination, the ultrasound is set on the contrast module, it is preferable the ultrasound to be in the B mode and the CE-IOUS to be displayed simultaneously (side-by-side). The contrast substance is prepared as a solution by adding powder and shaking it, after which it is injected intravenously, being quickly “captured” by the vascular system and giving the operator the opportunity to initiate the examination and record the process of capturing the contrast agent by the examined structures.

Figure 4. Contrast enhanced intraoperative ultrasound of a hepatocellular carcinoma barely visible in gray scale (left). Characteristic aspect of “wash out” in the delayed phase (right). (from personal files of the authors)

Due to the long process of carcinogenesis of HCC, neovascularization in small lesions may not be visible with routine imaging methods. The echogenicity of these lesions can often change, especially post-therapeutic (embolization, RFA), making it difficult to identify typical signs of malignancy: irregular and hypoechoic

margin at the periphery of the lesion (49,50).

Hypervascularization of visible HCC in the arterial phase and washout of the specific contrast agent in the portal phase, which continues in the late phase, are visible intraoperatively only with the help of CE-IUS (16). Torzzili et al classified the vascular pattern of HCC nodules evaluated during surgical procedures into four categories (51) (*Fig. 5*). Surgical resection is recommended for three of the four patterns the treatment plan being modified in 78% of cases after CE-IUS. (50) CE-IUS facilitates outlining the resection area and determining the dissection plane, resulting in easier resection guidance (24).

The technique has the advantage of being reproducible, it is not expensive, but it has the disadvantage that it depends on the experience of the examiner and the equipment used.

In ablative techniques, the CE-IUS plays a key role for the intraoperative verification of the post-ablation necrosis area, providing the possibility to repeat and complete the ablation when the situation requires it (52).

Figure 5. Classification of patterns of enhancement in CEIUS of those lesions detected in IUS during surgery for HCC. Lesions having a class A pattern, featured by a hyper vascular enhancement in early phase (A1-2), or any hypoechoic pattern in the delayed phases (A1-3), has to be resected; lesions showing a class B pattern of enhancement has no indication to be removed; (from Guido Torzilli. *Ultrasound-Guided Liver Surgery*. Springer. 2014) (24)

Intraoperative elastography

A newer method, as a practical applicability of IOUS is elastography, a non-invasive and non-irradiating technique that evaluates the elasticity of tissues in organs. It can be strain or shear wave type. Strain elastography is based on compression, being a qualitative method that is based on the deformation of the tissue produced by compression; thus, a color map is obtained and depending on this color code we can assess the probability of malignancy or benignity (*Fig. 6*). The second method (shear-wave) is a quantitative method that is based on recording the shear waves generated by compression; likewise, a color map is made, evaluated by values quantified in kilopascals (kPa) (53).

Elastography has currently established applications in transparietal ultrasound, especially in liver pathology to quantify the degree of fibrosis and less often for the differential diagnosis of liver tumors.

Intraoperative research shows that hepatic intraoperative elastography may have an additive role in intraoperative palpation (which is subjective, depending on the surgeon's experience) and practically replace it, especially in the case of small tumors, difficult to identify on a pathological liver, such as the cirrhotic one. (54)

The literature indicates that intraoperative elastography may be useful for the differential diagnosis of liver tumors (benign vs. malignant) and may even guide us to a diagnosis of primary tumors (HCC) or secondary tumors (metastases) (19,54). Unfortunately, in terms of the accuracy and sensitivity of elastography, reports shows that currently CE-IIOUS is clearly superior, with an accuracy of 94% versus 69% and even better results can be obtained by combining the two methods (55–57). The conclusions are quite clear in the literature, CE-IUOS being currently more sensitive than elastography and having an indication of first intention (58).

The role of elastography was also investigated in the evaluation of the necrotic area after ablation (59,60). The first studies

Figure 6. Intraoperative elastography of a hepatocellular carcinoma. (from personal files of the authors)

appeared in 2014 and showed that elastography cannot accurately describe the area after ablation (61). There are, however, more recent in vivo experimental models that suggest that elastography has potential in this field, which underscores the need for further research (62).

Perspectives

The continuous development of technology will of course lead to an increased use of IOUS by surgeons, offering the possibility of extending the indications for liver resections, with the ultimate goal that more patients will benefit from radical surgery, preserving as much functional parenchyma as possible.

CE-IIOUS already has a well-defined role, both for diagnosis and for evaluating the effectiveness of therapies. Progress could be made by improving current contrast agents based on nanoparticles (NP) and nanomedicine. The ideal contrast agent should accumulate selectively in the target tissue to improve image contrast, as NP can facilitate this transport. The introduction of designed microparticles or NP into theranostic biomedicine can substantially improve the imaging contrast/precision and enhance the therapeutic efficiency (63).

Elastography remains an easy and quick technique to be performed intraoperatively that could replace/improve the subjective palpation of the surgeon, especially in the case of intraparenchymal tumors. The potential benefits that it could bring intraoperatively are still subject of research.

Intraoperative fluorescence and advanced navigation techniques in which preoperative imaging is projected directly into the surgical site (virtual reality) are techniques already used in centers of excellence in the world. Even if the feasibility of these techniques is proven, the need for equipment and the currently high costs limits their large-scale implementation. The combination of these techniques with IOUS brings clear benefits through real-time 3D characterization of already identified lesions.

Conclusions

HCC represents a therapeutic challenge, often requiring personalized treatment due to the presence of liver cirrhosis that can limit radical treatments. Regardless of the chosen management, IOUS can play an extremely important role in the diagnosis and staging of the disease, with benefits and practical applications in the treatment of tumors, especially when contrast administration and elastography are associated. IOUS is indispensable for the surgeon when opting for a radical oncological treatment, through the contribution brought in guiding the surgical procedures (resection and/or ablation) and through the possibility of evaluating the effectiveness of the treatment at the time of surgery.

Conflict of interest

The authors have no conflict of interest.

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